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Professional paper

Evaluation of measurement uncertainty of the results from dissolution test of letrozole tablets using combined approaches

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Abstract

This paper presents two simple combined approaches for estimating measurement uncertainty of dissolution tests of tablets containing 2.5 mg letrozole. The first approach integrates a top-down approach based on data from the validation study with the data from the qualification of the dissolution apparatus. The second top-down approach combines the data from participation in PTS with the uncertainty related to standard and sample solutions preparation. Additionally, a bottom-up approach for estimating the measurement uncertainty was applied to identify the variability sources and to evaluate their contributions to the combined standard uncertainty. The results indicate that the main contributor to the combined standard uncertainty is the standard uncertainty related to the dissolution apparatus (81.5%), followed by the method precision (8.7%). Both combined approaches (validation data with instrument qualification and PTS data with the uncertainty of testing solutions) resulted in similar measurement uncertainty estimates to those obtained with the bottom-up approach, suggesting that either approach can be effectively used for uncertainty estimation, depending on data availability.

Key words: dissolution test, measurement uncertainty, bottom-up approach, combined top-down approach

Introduction

Letrozole ($C_{17}H_{11}N_5$) is a third-generation nonsteroidal aromatase inhibitor, used to treat certain types of breast cancer. Letrozole is a highly potent and selective inhibitor of the enzyme activity of intracellular aromatase, effectively blocking estrogen synthesis, and leading to the inhibition of the growth of hormone-responsive breast tumors *in vivo* (Bhatnagar, 2007). According to Ph.Eur. monograph (01/2024:2334), letrozole is a white to yellowish crystalline powder, practically insoluble in water, freely soluble in methylene chloride, and sparingly soluble in methanol (Council of Europe, current edition). Letrozole is classified as a BCS class I active pharmaceutical substance (API) and the recommendation for the dissolution test includes the use of the Paddle Method (apparatus 2, USP, Ph.Eur), 500 mL of 0.1N HCl in an aqueous medium, without surfactant at 37±0.5 °C, with stirring rate of 50 rpm and the dissolution criterion of Q=80% in 30 minutes (FDA, 2018, 2024; USP, current edition).

The dissolution test is one of the most critical tests in the pharmaceutical development, manufacturing and quality control of solid pharmaceutical dosage forms administered orally. This test is provided for testing the compliance of the solid dosage forms with the compendial requirements, providing insight into the bioavailability of

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the API from solid pharmaceutical dosage forms, quality of the medicinal product and consistency of the manufacturing process (Council of Europe, current edition; Hoener and Benet, 1990).

Development and validation of the dissolution test should ensure that the test is designed to generate data without high variability, to enable easy identification of the trends or effects of formulation changes. Sources of the variability of dissolution test results may be related to the formulation (e.g., active substance, excipients, or manufacturing process, poor content uniformity, process inconsistencies, excipient interactions or interference, coating, capsule shell ageing and hardening or softening of the dosage form during storage) or artefacts appearing in the test procedure (e.g., coning, tablets sticking to the vessel wall or basket screen) and the dissolution method and analytical procedure used for quantification (USP, current edition).

Measurement uncertainty is an essential parameter for interpreting the testing results, it is an indicator of the variability of analytical procedure and the validity of the testing results. It is a very important input for making the decision on compliance of tested samples and for establishing the criteria for the performance of the analytical procedure (Elison and Williams, 2012).

Estimation of the measurement uncertainty related to the dissolution test is necessary in cases when the measured dissolved fraction is close to the value of Q (quantity of API dissolved in a specified time, expressed as a percentage of the content stated on the product label (Council of Europe, current edition)), because the estimated uncertainty may affect the decision on compliance or non-compliance, in the development, validation and comparison of analytical procedures and for confirming out-of-specification results, especially in case when the test could not be repeated.

Several approaches for evaluating measurement uncertainty and variability of the dissolution test are described in the literature, including Monte Carlo simulations, ANOVA and bottom-up approach (Du, 2017; Romero and Lourenço, 2017; Siewert et al., 2002).

In the bottom-up approach, the uncertainty of each source is estimated and then the combined standard uncertainty is calculated from the individual uncertainty estimates (Joint Committee for Guides in Metrology (JCGM/WG1), 2008). In the top-down approach, the combined standard uncertainty is estimated directly using method performance data (e.g. validation study data, collaborative study data, proficiency testing study data, control charts, and data from testing certified reference materials) (Barwick and Ellison, 2000; Elison and Williams, 2012; OMCL Network/EDQM of the Council of Europe, 2020a, 2020b).

The objective of this study was to develop a simple, comprehensive, and reliable strategy for estimating the measurement uncertainty of dissolution test results for tablets containing 2.5 mg of letrozole. To achieve this, two combined approaches were applied: a top-down approach combining the data from a validation study and dissolution apparatus qualification, and another top-down approach using data from participation in a proficiency testing scheme (PTS) combined with uncertainty related to the preparation of testing solutions. Additionally, a bottom-up approach was employed to identify sources of variability and assess their contributions to the combined standard uncertainty.

Material and methods

Reagents, materials and equipment

Letrozole 2.5 mg film-coated tablets (purity 101.79%) were obtained from the market in the Republic of North Macedonia. Letrozole CRS, Ph.Eur. 99.9%, batch 5, was used as a reference standard. Hydrochloric acid (Thermo Fisher Scientific, UK) was used for preparation of the dissolution medium (0.1 M HCl). Methanol RS for HPLC isocratic grade ACS reag. Ph.Eur R2 and acetonitrile RS for HPLC, isocratic grade were obtained from Carlo Erba (Germany).

Measurements were performed on an analytical balance (Sartorius TE2109575, d=0.1 mg, Germany) calibrated and verified according to OMCL guidelines for the qualification of Balances (OMCL Network/EDQM of the Council of Europe, 2020c). Certified volumetric flasks (100 mL), pipettes (5 mL) and volumetric cylinder (500 mL) supplied by ISOLAB Laborgeräte GmbH, Germany, were used for the preparation of standard and sample solutions. SevenCompact pH meter S210 (Mettler Toledo, Greifensee, Switzerland) was used for the pH value adjustment of the dissolution medium. The dissolution test was performed on SOTAX AT7 Smart (Donau Lab Zurich, Switzerland). High-performance liquid chromatography was performed using a Shimadzu LCMS 8030, Nexera DAD/UPLC system equipped with an online degasser (DGU-20A Degasser), solvent delivery module (LC-30AD, Binary Pump) autosampler (SIL-30AC), column oven (CTO-20AC)), Photodiode Array detector (SPD-M20A) and software LabSolutions LCMS Version 5.41.

Preparation of the standard solution

An accurate weight (10 mg) of Letrozole CRS, was dissolved in acetonitrile ин a 100 mL volumetric flask, and diluted with the mobile phase. 5 mL of this solution was diluted to 100 mL with the dissolution medium to obtain the final concentration of 0.005 mg/mL.

Dissolution test

The dissolution test was conducted according to the USP monograph for Letrozole tablets, dissolution test 1 (Council of Europe, current edition; USP, current edition), using Apparatus 2 (Paddle apparatus) and 500 mL 0.1 N solution of HCl equilibrated to a 37±0.5 °C as dissolution medium, at a rotation speed of 100 rpm. The dissolution medium was de-aerated by heating the medium with gentle

stirring, to about 41 °C and immediately filtered under a vacuum (0.45 µm Nylon filter) with vigorous stirring. Six tablets containing letrozole 2.5 mg were tested individually. The sampling was performed after exactly 30 minutes and samples were analyzed on HPLC without further dilution.

Standard and sample solutions were filtrated with a nylon syringe filter pore size 0.45 µm.

Chromatographic conditions

Separation was performed on an analytical column Nucleosil 100 -5 C18, 50 x 4.6 mm; 5 µm, with isocratic elution, using a mixture of acetonitrile and water (48:52 *% V/V*) as a mobile phase, with a flow rate of 1 mL/min and the temperature of the column maintained at 25 °C. The injection volume was 20 µL. The detection was carried out at a wavelength of 230 nm.

Results and discussion

Specification of the measurand and identification of the uncertainty sources

The measurement result (measurand) is the quantity of dissolved letrozole expressed as per cent of the declared content (2.5 mg), calculated using equations (1):

$$\%\ letrozole = \frac{A_{smaple} \cdot m_{st} \cdot P_{st} \cdot V_{dil2} \cdot V_{diss} \cdot 100}{A_{st} \cdot V_{dil1} \cdot V_{dil3} \cdot declared\ content} \qquad (1)$$

where A_{smaple} and A_{st} are the peak areas of the sample and standard solution, $m_{st}\ and\ P_{st}$ are the weight and the potency of the reference substance letrozole. V_{dil} (1-3) are the dilution volumes for the preparation of the standard solution (100.0 mL, 5.0 mL, 100. 0 mL) and V_{diss} is the volume of the dissolution medium (500 mL). The obtained results (Table 1) comply with the requirements (Q=80%) (USP, current edition).

The relevant sources of uncertainty where identified using the equations (1) and are presented in a cause and effect diagram (Fig 1) (Ellison and Barwick, 1998; Kufelnicki et al., 2005).

Table 1. Amount of the dissolved letrozole, expressed as percentage of the declared content

Sample	% of the declared content
1	99.75
2	101.13
3	100.30
4	100.50
5	101.76
6	100.88

Quantification of combined standard uncertainty using the bottom-up approach

The measurement uncertainty of each contributor was quantified individually and then combined to calculate the combined standard uncertainty (bottom-up approach) (Elison and Williams, 2012; Joint Committee for Guides in Metrology (JCGM/WG1), 2008; OMCL Network/EDQM of the Council of Europe, 2020a, 2020b).

The standard uncertainty of the mass (R) of reference standard letrozole was calculated using the uncertainty of measurement of the weighing result (U_b, k=2, for approximately 95% level of confidence) stated on the balance calibration certificate (uncertainty of balance usage):

$$U_b = (1.26 \cdot 10^{-4} + 1.41 \cdot 10^{-5} \cdot R) \qquad (2)$$

In equation (2), R was replaced with the accurate weight of Letrozole CRS and the obtained value was divided by the coverage factor of 2.

Considering that the reference standard is certified reference material (Ph.Eur.) and the uncertainty of the assigned value was not stated on the certificate of analysis, it was considered to be negligible in line with the Ph.Eur. 5.12 (Council of Europe, current edition). The uncertainties related to the dilution volumes of the standard solution (100 mL and 5 mL) were calculated by combining the uncertainty from the calibration certificate $u_{(Vcal)}$, temperature expansion, $u_{(V_T)}$ and the uncertainty obtained from repeatability test of the volumetric flasks, $u_{(Vrep)}$, using following equation:

$$\frac{u(V)}{V} = \sqrt{\left(\frac{u(V_{cal})}{V}\right)^2 + \left(\frac{u(V_T)}{V}\right)^2 + \left(\frac{u(V_{rep})}{V}\right)^2} \qquad (3)$$

The volumetric flasks have been calibrated at 20°C, but the laboratory temperature usually varies between 16 °C and 24 °C (20 ±4 °C). The uncertainty from the temperature effect was calculated using equation (4), from the estimate of temperature range and the coefficient of volume expansion water (0.00021), assuming rectangular distribution (Elison and Williams, 2012).

$$u_{(V_T)} = \frac{V_{mL} \cdot 4°C \cdot 0.00021}{\sqrt{3}} \qquad (4)$$

The instrument's contribution to the uncertainty of the measurement ($u_{(instrument)}$) was calculated using equation (5), based on the precision results (standard deviation) obtained from the instrument's most recent periodic qualification, assuming triangular distribution.

$$u_{(instrument)} = \frac{SD_{(periodic\ qualification)}}{X_{average\ \%\ released}} \qquad (5)$$

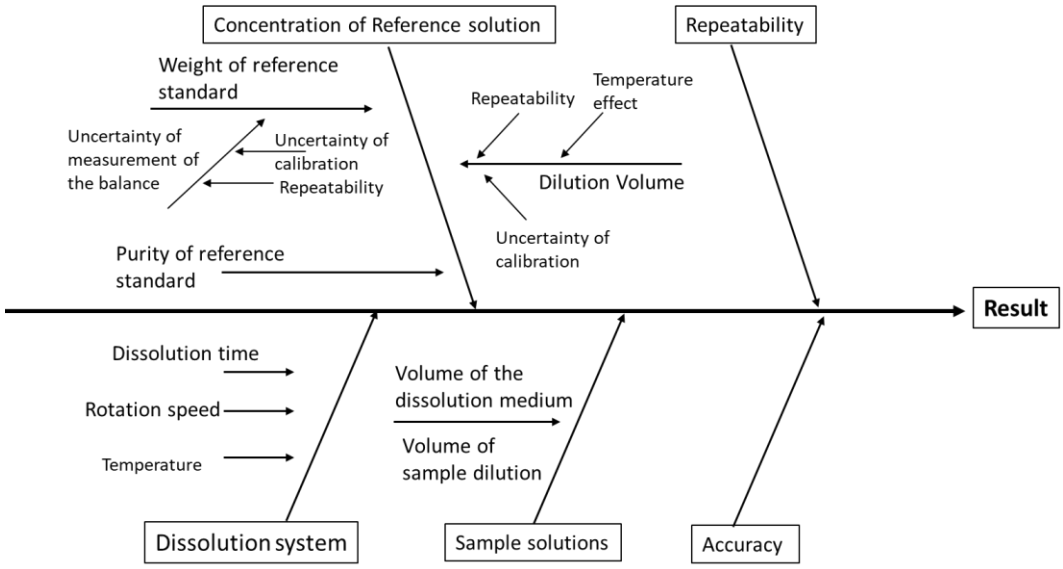

Fig. 1. Cause-effect diagram of the uncertainty sources for the dissolution test.

Table 2. Calculated values for each uncertainty source

Symbol	Description	Value	u	Relative u
$u_{m_{(St)}}$	Mass of Letrozole	9.6 mg	0.063068 mg	0.00657
$u_{V1_{(dil.1)}}$	Dilution volume 1	5.0 mL	0.01279 mL	0.00256
$u_{V2_{(dil.2)}}$	Dilution volume 2	100.0 mL	0.06361 mL	0.00063
$u_{V_{(diss)}}$	Volume of dissolution medium	500 mL	2.260 mL	0.00452
$u_{precision_{(HPLC)}}$	HPLC precision, AUC_{St} (n=6)	598520.6 mAU·s	834.908 mAU·s	0.00139
$u_{precision_{(val)}}$	Method precision			0.0133
$u_{(instrument)}$	Instrument qualification			0.0230
u_c	*Expanded uncertainty*			

Table 3. Expanded uncertainty estimated using bottom-up approach and range of the results from the dissolution test

Sample	% of the declared content	u_c	U (95% confidence interval)	Range % of the declared content	
1	99.75	2.8	5.6	105.3	94.2
2	101.13	2.8	5.7	106.8	95.5
3	100.30	2.8	5.6	105.9	94.7
4	100.50	2.8	5.6	106.1	94.9
5	101.76	2.8	5.7	107.4	96.1
6	100.88	2.8	5.6	106.5	95.2

$$\frac{u_c}{\%\ dissolved\ Letrozole/tbl} = \sqrt{\left(\frac{u_{m_{(St)}}}{m_{(St)}}\right)^2 + \left(\frac{u_{V1_{(dil.1)}}}{V1_{(dil.1)}}\right)^2 + 2\left(\frac{u_{V2_{(dil.2)}}}{V2_{(dil.2)}}\right)^2 + \left(\frac{u_{V_{(diss)}}}{V_{(diss.)}}\right)^2 + \left(\frac{u_{precision_{(HPLC)}}}{Average_{(HPLC)}}\right)^2 + \left(\frac{u_{precision_{(val)}}}{Average_{(val.prec)}}\right)^2 + \left(\frac{u_{(instrument)}}{\sqrt{6}}\right)^2} = 0.0279 \quad (6)$$

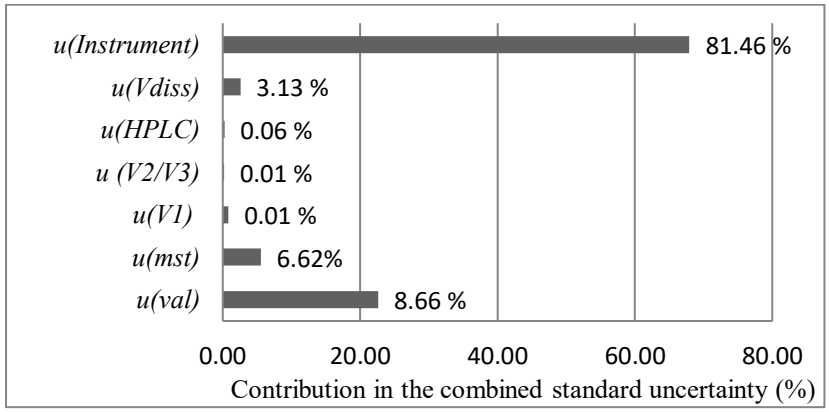

Fig. 2. Contribution of each uncertainty source to combined standard uncertainty.

The combined standard uncertainty (u_c) was calculated by combining the uncertainty estimates for each contributor, expressed as relative standard uncertainties. This calculation was performed using equation (6), considered as the uncertainty associated with the whole analytical procedure, expressed as an effect on the final result (Elison and Williams, 2012).

$u_{precision_{(HPLC)}}$ was estimated from the standard deviation of the peak area from system suitability results, whereas $u_{precision_{(val)}}$ was estimated according to the OMCL guideline for evaluation of measurement uncertainty Annex 2.

Expanded uncertainty $U_{(\%\ dissolved\ Letrozole/tbl)}$ was calculated by multiplying the combined uncertainty by a coverage factor (k=2), corresponding to an approximate 95% confidence level. Table 2 provides a summary of the relative standard uncertainties for each contributor.

The expanded uncertainty of the dissolution test of letrozole was obtained by multiplying the combined uncertainty (u%) by a coverage factor k=2, for an approximately 95% confidence level.

$$U = u_c \cdot 2$$

The results for expanded uncertainty estimated using bottom-up approach and range of the results from the dissolution test are shown in Table 3.

The estimates for standard uncertainty of each individual source were used for evaluation of the contributions of each uncertainty source to the combined standard uncertainty (Fig. 2).

From Fig. 2 it is evident that the main contributor to the combined standard uncertainty is the standard uncertainty related to the dissolution apparatus (81.5%), followed by the method precision (8.7%), the contribution of the mass of the reference standard (6.6%) and the uncertainty of the dissolution medium volume (3.13%). The uncertainty contributions related to the dilution volume and the HPLC system precision can be considered negligible (less than one-third of the major contributor) (Elison and Williams, 2012). By applying the combined top-down approach, the combined contribution to the uncertainty of the result was estimated using method performance data (data from validation study and data from participation in PTS) with the most relevant sources of uncertainty.

Quantification of combined standard uncertainty using combined top-down approach based on data from method validation

Considering that the results are obtained by strictly following analytical procedure, system suitability criteria were fulfilled and comparable precision of the obtained results with the data from the validation study was demonstrated, data from method validation (method precision) in combination with the uncertainty arising from the instrument qualification were applied directly for estimation of the combined standard uncertainty of the result. The standard uncertainty estimate based on validation data (precision and bias) accounts for the uncertainty associated with the analytical procedure, including the preparation of the standard and sample solutions, as well as the volume of the dissolution medium. However, since the method validation was conducted in a different laboratory, the uncertainty related to instrument qualification, identified as the major source of uncertainty must also be included in the total uncertainty budget (Elison and Williams, 2012; OMCL Network/EDQM of the Council of Europe, 2020b). The combined standard uncertainty was calculated using the following formula:

$$u_c = \sqrt{u_{(precision)}{}^2 + u_{(bias)}{}^2 + \left(\frac{u_{(instrument)}}{\sqrt{6}}\right)^2} = 0.0278 \qquad (7)$$

where: $u_{(precision)}$= 0.013 is the uncertainty contribution associated with the precision and $u_{(bias)} = 0.0082$ is the uncertainty contribution associated with the bias calculated according to the OMCL guideline Annex 2 (OMCL Network/EDQM of the Council of Europe, 2020a). The results are shown in Table 4.

Quantification of combined standard uncertainty using the combined top-down approach based on data from participation in PTS

When using the top-down approach, based on data from Proficiency Testing Studies (PTS), the combined standard uncertainty can be estimated using the laboratory's own data: repeatability of the test results can be used as an estimate for the precision and the z-score value can be used as an estimate for the bias (Eurolab, 2007; OMCL Network/EDQM of the Council of Europe, 2020b). In this study, the data from single participation in the PTS studies for dissolution test organized by the European Directorate on the Quality of Medicines (EDQM), Council of Europe, were used (Miller and Miller, 2010). The standard uncertainty was calculated according to the equation:

$$u_c = \sqrt{S^2_{within-lab}} \qquad (8)$$

where: $S_{within-lab}$ is the standard deviation of the test results (three independent determinations).

The laboratory has shown satisfactory results in the proficiency test round (z-score≤2), therefore the bias was not included in the calculation as considered negligible (OMCL Network/EDQM of the Council of Europe, 2020b). The uncertainty estimate from participation in PTS accounts for the uncertainty related to the dissolution apparatus, which is the most relevant contributor to the combined measurement uncertainty. However, the analytical procedure differs in dissolution volume and standard solution preparation compared to the dissolution test for letrozole tablets. Therefore the combined standard uncertainty was calculated by combining the standard uncertainty from PTS ($\frac{u_c}{x}PTS$) with the contribution of the mass of the reference standard $u_{m_{(St)}}$ and the uncertainty of the dissolution medium ($u(Vdiss)$ previously identified as relevant sources, using the following equation (9):

$$\frac{u_c}{\%_{of\ the\ decl.\ content}} = \sqrt{\left(\frac{u_{m_{(St)}}}{m_{(St)}}\right)^2 + \left(\frac{u(Vdiss)}{V_{diss}}\right)^2 + (\frac{u_c}{x}PTS)^2} = 0.0279 \qquad (9)$$

The results for combined and the expanded uncertainties estimated using data from participation PTS and uncertainty of preparation of testing solutions are shown in Table 5.

The obtained results show that both combined approaches (validation data/instrument qualification or data from participation in PTS/uncertainty of preparation of testing solutions) can be equally applied for the estimation of measurement uncertainty, depending on the available data. The bottom-up approach provides more details into the effect of different sources on the measurement uncertainty and may help in understanding the sources of the variability of the method. This approach can be used when the relevant data for the method performance is not available, during the method development, or investigation of out-of-specification or out-of-trend results.

Table 4. Expanded uncertainty estimated using a combined top-down approach (Data from method validation/Instrument qualification) and range of the results from the dissolution test

Sample	% of the declared content	u_c	U (95% confidence interval)	Range % of the declared content	
1	99.75	2.8	5.6	105.3	94.2
2	101.13	2.8	5.6	106.8	95.5
3	100.30	2.8	5.6	105.9	94.7
4	100.50	2.8	5.6	106.1	94.9
5	101.76	2.8	5.7	107.4	96.1
6	100.88	2.8	5.6	106.5	95.3

Table 5 Expanded uncertainty estimated using combined top-down approach (data from participation in PTS and uncertainty of preparation of testing solutions) and range of the results from the dissolution test

Sample	% of the declared content	u_c	U (95% confidence interval)	Range % of the declared content	
1	99.8	2.8	5.6	105.3	94.2
2	101.1	2.8	5.7	106.8	95.5
3	100.3	2.8	5.6	105.9	94.7
4	100.5	2.8	5.6	106.1	94.9
5	101.8	2.9	5.7	107.5	96.1
6	100.9	2.8	5.7	106.5	95.2

Conclusion

The relevant sources of variability in the dissolution test of letrozole tablets were identified using the bottom-up approach for estimating measurement uncertainty. The major contributor to the combined standard uncertainty was the dissolution apparatus (81.5%), followed by method precision (8.7%) and analytical procedure for preparation of the standard solution (weight of the reference substance) and sample solutions (volume of the dissolution medium).

Additionally, two simple and practical combined top-down approaches for estimating measurement uncertainty in dissolution tests of tablets containing 2.5 mg letrozole were presented. The first top-down approach combines the data from the validation study with the data from the qualification of the dissolution apparatus, while the second combines data from participation in PTS with uncertainty related to standard and sample solution preparation. Both approaches resulted in uncertainty estimates comparable with the bottom-up approach, and can be effectively applied for estimation of the measurement uncertainty in dissolution testing, depending on the available data.

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OMCL Network/EDQM of the Council of Europe, 2020a. Evaluation of Measurement Uncertainty Annex 2: Estimation of Measurment Uncertainty Using Top-down Approach Annex 2.1: Use of Data from Validation Studies for the Estimation of Measurement Uncertainty (PA/PH/OMCL (18) 149 R1), 1–10.

OMCL Network/EDQM of the Council of Europe, 2020b. Evaluation of Measurement Uncertainty Annex 2: Estimattion of Measurment Uncertainty Using Top-down Approach Annex 2.5: Use of Data from Proficiency Testing Studies for the Estimation of Measurement Uncertainty (PA/PH/OMCL (18) 153 R1 CORR), 1–17.

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Резиме

Евалуација на мерната неодреденост на резултатите од тест за растворливост на таблети летрозол со користење на комбинирани пристапи

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Клучни зборови: тест за растворливост, мерна неодреденост, *bottom-up* пристап, комбиниран *top-down* пристап

Во овој труд се претставени два едноставни комбинирани пристапи за проценка на мерната неодреденост на тестовите за растворливост на таблети што содржат 2.5 mg летрозол. Првиот пристап интегрира *top-down* пристап, базиран на податоци од студијата за валидација, со податоците од квалификацијата на апаратот за растворливост. Вториот *top-down* пристап ги комбинира податоците од учеството во PTS со неодреденоста поврзана со подготовката на стандардните и пробните раствори. Дополнително, беше применет и *bottom-up* пристап за проценка на мерната неодреденост, со цел да се идентификуваат изворите на варијабилност и да се евалуира нивниот придонес во комбинираната стандардна неодреденост. Резултатите покажуваат дека главен придонесувач во комбинираната стандардна неодреденост е стандардната неодреденост поврзана со апаратот за растворливост (81,5%), по што следи прецизноста на методот (8,7%). Двата комбинирани пристапи (податоци од валидација со квалификација на инструментот и PTS податоци со неодреденоста на испитуваните раствори) доведоа до слични проценки на мерната неодреденост како и *bottom-up* пристапот, што укажува на тоа дека секој од пристапите може ефикасно да се користи за проценка на неодреденоста, во зависност од достапноста на податоците.